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FILING RECEIPT DATED FOR FEBRUARY 11, 2004.
SERIAL NUMBER: 60/459,864
FILING DATE: April 02, 2003

PRIORITY DOCUMENT
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CONFIRMATION NO. 7294

CORRECTED FILING RECEIPT

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THOMAS HOXIE
NOVARTIS, CORPORATE INTELLECTUAL PROPERTY
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Date Mailed: 02/11/2004

Receipt is acknowledged of this provisional Patent Application. It will not be examined for patentability and will become abandoned not later than twelve months after its filing date. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Filing Receipt Corrections, facsimile number 703-746-9195. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

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Non-Publication Request: No

Early Publication Request: No

Title

Organic compounds

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January 05, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: *60/459,864*
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Ferenc Stefanie Markus	Martenyi Zechner Schmutz	, , ,

TITLE OF THE INVENTION (280 characters max)

ORGANIC COMPOUNDS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☒ Specification (Including Any Claims) - 13 pages
- ☐ Drawings - sheets
- ☐ Other (specify):

METHOD OF PAYMENT

The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-0134 in the name of Novartis Corporation.	PROVISIONAL FILING FEE AMOUNT: $ 160

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Respectfully submitted,

Date: April 2, 2003

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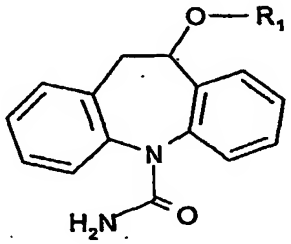
Organic Compounds

The present invention relates to new pharmaceutical uses of 10-hydroxy-10,11-dihydrocarbamazepine derivatives and combinations comprising said compounds.

In particular, the invention relates to a method for the treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I



(I)

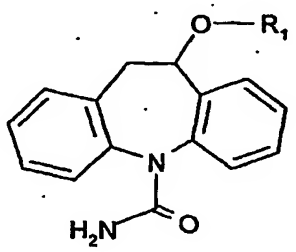
wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl, alone or in combination with further therapeutically active compounds as specified herein.

The preparation of the compound of formula I wherein R_1 is hydrogen and its pharmaceutically acceptable salts is described, e.g., in US 3,637,661. Such compound, monohydroxycarbamazepine, (10-hydroxy-10,11-dihydro-carbamazepine), the main metabolite of the antiepileptic oxcarbazepine (Trileptal ®) is well known from the literature [see for example Schuetz H. et al., Xenobiotica (GB), 16(8), 769-778 (1986)]. The compound is indicated to be suitable for the treatment of psychosomatic disturbances, epilepsy, trigeminal neuralgia and cerebral spasticity.

The preparation of the compound of formula I wherein R_1 is C_1-C_3alkyl carbonyl and its pharmaceutically acceptable salts is described, e.g., in US 5,753,646. The compounds are described to be efficacious against epilepsy.

In accordance with the present invention, it has now surprisingly been found that a compound of formula I and the pharmaceutically acceptable salts thereof is also useful for the treatment of affective disorders.

Hence, the present invention provides a method for the treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

Furthermore, the present invention relates to a method for the treatment of affective disorders, for example severe acute mania or bipolar disorders, in a subject in need of such treatment, which comprises administering to said subject every 20 to 28 hours an amount between about 600 and about 3000 mg, preferably between 750 and 2500 mg, or, in the case of severe acute mania, between 1500 and 2500 mg of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

Additionally, the present invention pertains to a method for the maintenance treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

In one embodiment, the present invention pertains to a method for the maintenance treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject every 20 to 28 hours an amount between about 600 and about 2500 mg, preferably between 750 and 1250 mg, of a compound of formula I wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

In one preferred embodiment of the present invention, R_1 represents hydrogen.

In preferred another embodiment of the present invention, R_1 represents acetoxy.

The term "affective disorders" as used herein includes, but is not limited to depression and uni- and bipolar disorders, e.g. manic-depressive psychoses, pre-menstrual dysphoric disorder, post-partum depression, post-menopausal depression, neurodegeneration-related depressive symptoms and depression occurring following cessation of psychostimulant intake, extreme psychotic states, e.g. mania, schizophrenia, and excessive mood swings where behavioural stabilization is desired.

Administration "every 20 to 28 hours" means preferably administration every 22 to 26 hours, more preferably about every 24 hours.

The pharmacological activity of a compound of formula I may, for example, be demonstrated in clinical studies. Such clinical studies are preferably randomized, double-blind, clinical studies in patients with affective disorders comprising administering a compound of formula I wherein R_1 is hydrogen in a daily dose between 750 and 2500 mg. The beneficial effects on affective disorders can be determined directly through the results of these studies or by changes in the study design which are known as such to a person skilled in the art.

The activity of the compound of formula I in the treatment of affective disorders treatment is also evidenced, for example, in tests suitable for detecting drugs having potential behavioural desinhibitory and/or sociotropic effects which are thought to be relevant for recovery from social withdrawal, a cardinal feature of depression and related psychiatric conditions. For instance, drug effects on social withdrawal of intruder mice can be evaluated by using the basic method as described in Triangle, 1982, 21:95-105 and J. Clin. Psychiatry, 1994, 55:9 (suppl. B) 4-7.

Furthermore, the activity of the compound of formula I in the treatment of affective disorders treatment can be evidenced in the Vogel conflict test. The Vogel conflict test is the standard test to detect psychiatric, mainly anxiolytic and antidepressant drug action since various classes of anxiolytic and antidepressant drugs are effective in this test and since there is a high co-morbidity between anxiety states and other psychiatric, e.g., depression disorders. The very surprising high efficacy of a compound of formula I, in particular oxcarbazepine, in this test is therefore indicative of drug activity in depression or other affective disorders as defined above.

For the treatment of conditions associated with affective disorders, appropriate dosage will of course vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. In larger mammals, for example humans, an indicated daily dosage is in the ranges as provided above, conveniently administered, for example, in divided doses up to four times a day.

The compounds may be administered in any usual manner, e.g. orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injection solutions or suspensions.

The present invention also provides pharmaceutical compositions comprising the compounds in association with at last one pharmaceutical carrier or diluent for use in the treatment of affective disorders. Such compositions may be manufactured in conventional manner.

Unit dosage forms may contain for example from about 2.5 mg to about 1000 mg of the compound, preferably about 300 or 600 mg.

The invention further provides the use of a compound of formula I for the manufacture of a pharmaceutical composition for the treatment of affective disorders.

For the treatment of affective disorders a compound of formula I can be administered alone or in combination with at least one compound selected from the group consisting of lithium, valproic acid sodium salt, conventional antipsychotics, atypical antipsychotics, lamotrigine and antidepressants, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, and optionally at least one pharmaceutically acceptable carrier.

The term "lithium" as used herein includes, but is not limited to lithium acetate, lithium carbonate, lithium chloride, lithium citrate and lithium sulfate. The term "conventional antipsychotics" as used herein includes, but is not limited to haloperidol and fluphenazine. The term "atypical antipsychotics" as used herein includes, but is not limited to *olanzapine*, *quetiapine* and *risperidone*. The term "antidepressants" as used herein includes, but is not

limited to selective serotonin reuptake inhibitors (SSRI's). An SSRI's suitable for the present invention is especially selected from fluoxetine, *fuvoxamine*, sertraline, paroxetine and *escitalopram*.

Lithium acetate can be administered, e.g., in the form as marketed, e.g. under the trademark Quilonorm™. Lithium carbonate can be administered, e.g., in the form as marketed, e.g. under the trademark Eskalith™. Lithium citrate can be administered, e.g., in the form as marketed, e.g. under the trademark Litarex™. Lithium sulfate can be administered, e.g., in the form as marketed, e.g. under the trademark Lithium-Duriles™. Valproic acid sodium salt can be administered, e.g., in the form as marketed, e.g. under the trademark Divalproex Sodium™. Haloperidol can be administered, e.g., in the form as marketed, e.g. under the trademark Haloperidol STADA™. Fluphenazine can be administered, e.g., in the form of its dihydrochloride as marketed, e.g. under the trademark Prolixin™. Lamotrigine can be administered, e.g., in the form as marketed, e.g. under the trademark Lamictal™. Fluoxetine can be administered, e.g., in the form of its hydrochloride as marketed, e.g. under the trademark Prozac™. Paroxetine can be administered, e.g., in the form as marketed, e.g. under the trademark Paxil™.

The structure of the active agents identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. For example, sertraline can be prepared as disclosed in US 4,536,518 to Pfizer.

The pharmacological activity of a combination as disclosed herein may, for example, be demonstrated in clinical studies. Such clinical studies are preferably randomized, double-blind, clinical studies in patients with affective disorders. Such studies demonstrate, in particular, the synergism of the active ingredients of the combination as disclosed herein. The beneficial effects on affective disorders can be determined directly through the results of these studies or by changes in the study design which are known as such to a person skilled in the art. The studies are, in particular, suitable to compare the effects of a monotherapy using the active ingredients and those of a combination as disclosed herein.

Hence, the present invention pertains also to a combination comprising a compound of formula I, and at least one compound selected from the group consisting of lithium, divalproex, conventional antipsychotics, atypical antipsychotics, lamotrigine and anti-depressants, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use, especially for use in a method of treating affective disorders.

Such a combination can be a combined preparation or a pharmaceutical composition.

The term "a combined preparation", as used herein defines especially a "kit of parts" in the sense that the first and second active ingredient as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the ingredients, i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the active ingredients. The ratio of the total amounts of the active ingredient 1 to the active ingredient 2 to be administered in the combined preparation can be varied, e.g., in order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the first and second active ingredient, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutical effect in a non-effective dosage of one or both of the first and second active ingredient, and especially a strong synergism the first and second active ingredient.

Hence, the present invention also provides

- the use of a combination as disclosed herein for the preparation of a medicament for the treatment of affective disorders; and
- a commercial package comprising a combination as disclosed herein together with instructions for simultaneous, separate or sequential use thereof in the treatment of affective disorders.

When the combination partners employed in the combinations as disclosed herein are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the package insert of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise. In particular, the following dosages can be administered to the patient:

A combination comprising a compound of formula I, and at least one compound selected from the group consisting of lithium, divalproex, conventional antipsychotics and atypical antipsychotics, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use, is especially useful for the treatment of mania.

A combination comprising a compound of formula I, and at least one antidepressants, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use, is especially useful for the treatment of bipolar disorders.

Haloperidol may be administered to a patient in a total daily dosage of between about 5 to about 100 mg.

Lithium can be administered to a patient in a total daily dosage of between about 0.5 to about 1 g.

Olanzapine can be administered to a patient in a total daily dosage of between about 10 to about 20 mg.

Quetiapine can be administered to a patient in a total daily dosage of between about 500 to about 600 mg.

Risperidone may be administered to a patient in a total daily dosage of between about 2 to about 6 mg.

Valproic acid sodium salt may be administered to a patient in a total daily dosage of between about 2000 to about 3000 mg.

The following Examples serve to illustrate the invention without limiting the invention in its scope.

Example 1: Vogel Conflict Test

a) Description of method: The method, which detects anxiolytic and related other psychiatric activity, follows that described by Vogel et al, Psychopharmacologia 1971;21:1-7 Anxiolytics and antidepressants (e.g., Fontana et al., Psychopharmacology 1989;98(2):157-62) of various classes increase punished drinking.
Rats are deprived of water for 48 hours and are then placed individually into a transparent Plexiglas enclosure (15 x 32 x 34 cm) with a floor consisting of stainless steel bars (0.4 cm) spaced 1 cm apart. The back wall of the enclosure is made of opaque Plexiglass thereby concealing the observer from the experimental animal. In the centre of the opposite wall, 5 cm above the floor, a metal water spout protrudes into the cage and is connected to one pole of a shock generator (Apelex : Type 011346). The other pole of the shock generator is connected to the metal grid floor. The rat is left to explore until it found the water spout. Then, every time it drinks, it receives a slight electric shock (1.7 mA, 1 sec.) 2 seconds after it starts lapping. The number of shocks received (punished drinkings) is counted during a 3 minute period. 15 rats are studied per group. The test is performed blind. Compounds are evaluated at 50, 100 and 200 mg/kg, administered p.o. 60 minutes before the test, and compared with a vehicle control group. Clobazam (64 mg/kg), administered under the same experimental conditions, is used as reference substance. All substances are evaluated within the same experiment and compared with the same vehicle and reference substance controls. Data are analyzed by comparing treated groups with vehicle control using unpaired Student's t tests. The results are summarized in Table 1.

TABLE 1

EFFECTS OF OXCARBAZEPINE AND CLOBAZAM IN THE VOGEL CONFLICT TEST IN THE RAT

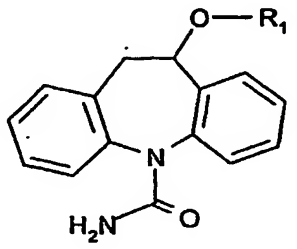
(15 RATS PER GROUP)

M3 (mg/kg) p.o. -60 min	PUNISHED DRINKING (number of shocks)		
	mean ± s.e.m.	p value	% change from control
Vehicle	4.4 ± 0.2	-	-
50	5.9 ± 0.5 *	0.012	+34%
100	8.4 ± 1.0 ***	0.001	+91%
200	10.4 ± 1.5 ***	0.001	+136%
CLOBAZAM 64 mg/kg p.o. -60 min	8.2 ± 1.1 **	0.003	+86%

Student's t test : * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

CLAIMS

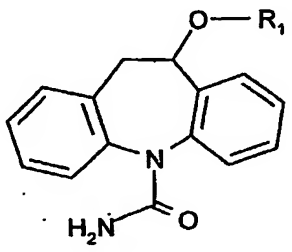
1. A method for the treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

2. A method for the treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject every 20 to 28 hours an amount between about 600 and about 3000 mg of a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

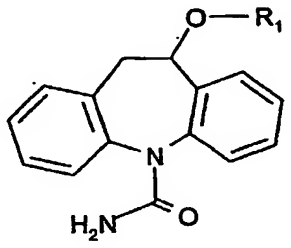
3. The method according to claim 2, wherein every 20 to 28 hours an amount between 750 and 2500 mg of a compound of formula I is administered.

4. The method according to claim 2, wherein the disorder is severe acute mania.

5. The method according to claim 4, wherein every 20 to 28 hours an amount between 1500 and 2500 mg of a compound of formula I is administered.

6. The method according to claim 2 or 3, wherein the disorders are bipolar disorders.

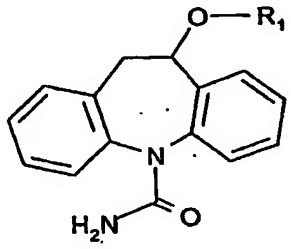
7. A method for the maintenance treatment of affective disorders in a subject in need of such treatment, which comprises administering to said subject every a therapeutically effective amount of a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

8. A method for the maintenance treatment of affective disorders in a subject in need of such treatment, which comprises administering every 20 to 28 hours to said subject an amount between about 600 and about 2500 mg of a compound of formula I



(I)

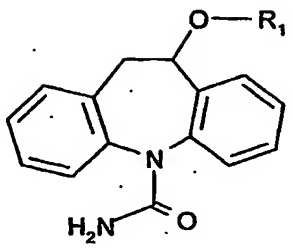
wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl.

9. The method according to claim 8, wherein every 20 to 28 hours an amount between 750 and 1250 mg of a compound of formula I is administered.

10. The method according to claim 2, 8 or 9 wherein R_1 represents hydrogen.

11. The method according to claim 1, 2, 7 or 8 wherein R_1 represents acetoxy.

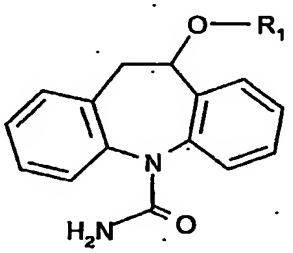
12. The use of a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl or a pharmaceutically acceptable salt thereof, for the treatment of affective disorders.

13. The use of a compound of I

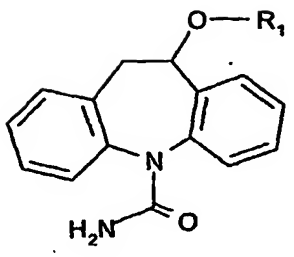


(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment of affective disorders.

14. The use according to claim 12 or 13 wherein R_1 represents acetoxy.

15. A pharmaceutical composition which incorporates as active agent a compound of formula I

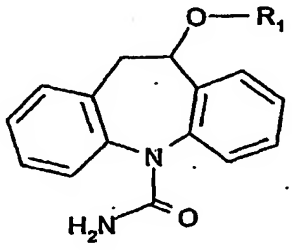


(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl or a pharmaceutically acceptable salt thereof, for use in the treatment of affective disorders.

16. A combination comprising

(a) a compound of formula I



(I)

wherein R_1 represents hydrogen or C_1-C_3alkyl carbonyl, and

(b) at least one compound selected from the group consisting of lithium, divalproex, conventional antipsychotics, atypical antipsychotics, lamotrigine and antidepressants,

in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt,

and optionally at least one pharmaceutically acceptable carrier.

17. Use of a combination according to claim 16 for the preparation of a medicament for the treatment of affective disorders.

18. A commercial package comprising a combination according to claim 16 together with instructions for simultaneous, separate or sequential use thereof in the treatment of affective disorders.